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Health Effects Assessment for Aldrin

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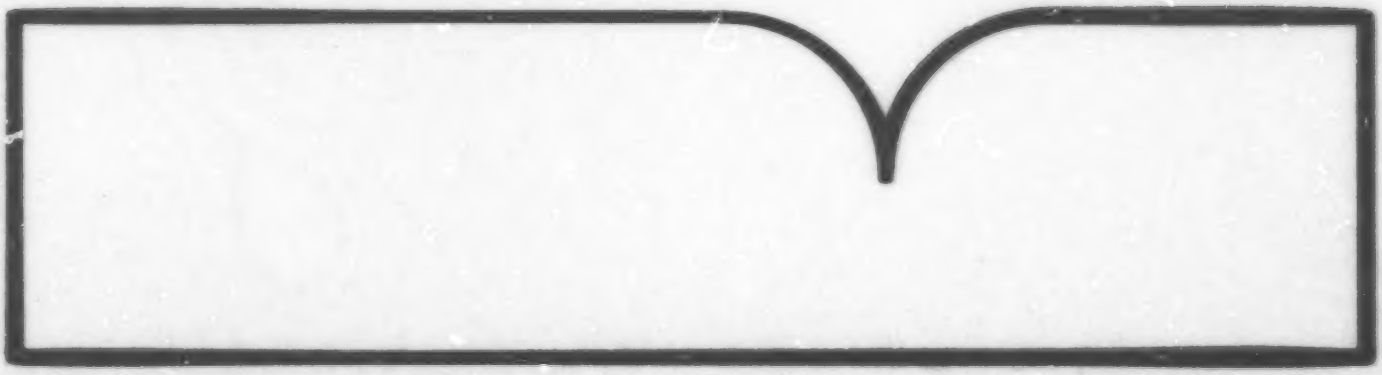

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HEALTH EFFECTS ASSESSMENT FOR ALDRIN

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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with aldrin. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary reflecting limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on line literature searches of the TOXLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Aldrin/Dieldrin. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-018. NTIS PB81-117301.

U.S. EPA. 1980b. Hazard Profile for Aldrin. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1986b. Carcinogenicity Assessment of Aldrin and Dieldrin. December 1986 Review Draft. Office of Health and Environmental Assessment, Carcinogen Assessment Group, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980c) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980c). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents to this series as well as the appropriate interpretation and use of the quantitative estimates presented.

The risk assessment for aldrin is based on positive results in three carcinogenicity bioassays using mice (NCI, 1977; Davis and Fitzhugh, 1962; Epstein, 1975; Davis, 1965). The U.S. EPA (1986a) calculated a human carcinogenic potency factor (q_1^*) of 17 $(mg/kg/day)^{-1}$ based on a dose-related increase in the incidence of hepatocellular carcinomas in male B6C3F1 mice and in both male and female CH_3 mice given aldrin in the diet for up to 2 years. The geometric mean of the three potency estimates was calculated as the best upper bound estimate on risk by U.S. EPA (1986b).

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LIST OF ABBREVIATIONS

CAS	Chemical Abstract Service
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
LOAEL	Lowest-observed-adverse-effect level
MFO	Mixed function oxidase
OMPA	Octamethyl pyrophosphoramide
ppm	Parts per million
RfD	Reference dose
RfD_S	Subchronic reference dose
TLV	Threshold limit value

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected chemical and physical properties and environmental fate of aldrin are presented in Table 1-1.

Considering its relatively low vapor pressure and high K_{oc} value, adsorption of aldrin to airborne particulates may occur. Vapor phase aldrin may react with hydroxyl radicals with an estimated half-life of $\leq$1 hour (HSDB 1986). Available data indicate that volatilization, oxidation by hydroxyl radicals, bioconcentration and adsorption to sediments will be significant in water (HSDB, 1986). The aquatic half-life of 34 days for aldrin is based on a study with lake water (Zoetemann et al., 1980). In both soil and water, dieldrin is reported to be a major degradation product of aldrin (Callahan et al., 1979; Sanborn et al., 1977). The half-life of aldrin in soil was estimated from persistence data (Adams, 1967) and the observation that after five annual applications of aldrin to soil, 95% disappeared in 1 year (Sanborn et al., 1977).

TABLE 1-1

Selected Chemical and Physical Properties and Half-lives for Aldrin

Property	Value	Reference
CAS number:	309-00-2	
Chemical class:	chlorinated pesticide	
Molecular weight:	364.93	
Vapor pressure:	2.31×10^{-5} mm Hg at 20°C	Sanborn et al., 1977
Water solubility:	2.7×10^{-2} mg/ℓ at 20°C	Sanborn et al., 1977
Log octanol/water partition coefficient:	3.01-7.40	Lu and Metcalf, 1975; Briggs, 1981
Bioconcentration factor:	10^3 to 10^4, various aquatic organisms	Callahan et al., 1979
Soil adsorption coefficient:	407-28,200	Sabljic, 1984
Half-lives:		
Water	34 days (lake)	Zoetemann et al., 1980
Soil	3-7 months	Adams, 1967; Sanborn et al., 1977

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Qualfe and Fitzhugh (1967) reported that aldrin was readily absorbed from the gastrointestinal tract. No quantitative data for absorption were available.

2.2. INHALATION

Pertinent data concerning the absorption of aldrin from the respiratory tract could not be located in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. NCI (1977) conducted subchronic range-finding studies with rats and mice. Groups of five male and five female Osborne-Mendel rats and equal numbers of B6C3F1 mice were fed diets containing aldrin in 2-fold increasing concentrations from 40-320 ppm (rats) or 2.5-80 ppm (mice) for 6 weeks followed by a 2-week observation period. In rats, some mortality and depression of body weight gain occurred at 160 and 320 ppm, but no such effects occurred at 40 and 80 ppm. All mice exposed to 40 and 80 ppm died, while two of those at 20 ppm died. No body weight effects occurred in any group. No other parameters of toxicity were monitored in these studies.

In a long-term oral toxicity study using dogs, Fitzhugh et al. (1964) orally treated 12 mongrel dogs with aldrin at dosages of 0.2, 0.5, 1 or 5 mg/kg/day (presumably in the diet), 6 days/week for up to 25 months. Gross toxic effects, including weight loss and convulsions, occurred at $\geq$0.5 mg/kg/day. Fatty degenerative changes in liver and kidney, and bone marrow changes (reduced cellularity) occurred at $\geq$1.0 mg/kg/day. No adverse effects were observed at $\geq$1.0 mg/kg/day or at 0.2 mg/kg/day. In another study, Deichmann et al. (1968) fed three groups of six male beagle dogs capsules containing 0.6 mg/kg aldrin, 0.3 mg/kg aldrin plus 12 mg/kg DDT, or 24 mg/kg DDT only, 5 days/week for 10 months. Signs of intoxication (hyper-excitability, tremors, anorexia) and some mortality occurred in both groups receiving aldrin.

3.1.2. Inhalation. Subchronic inhalation data could not be located in the available literature.

3.2. CHRONIC

3.2.1. Oral. Jager (1970) monitored workers at a pesticide manufacturing plant and reported that 33.2 µg/kg/day can be tolerated by workers for up to 15 years. The route of exposure was presumed to be oral. Some workers could tolerate twice this level without any signs of intoxication.

Treon and Cleveland (1955) conducted a study in which groups of 40 male and 40 female Carworth rats were fed diets containing aldrin at 0, 2.5, 12.5 or 25 ppm for 2 years. Mortality of females was significantly increased relative to controls at all concentrations tested; however, the authors questioned the validity of this observation because of unusually low mortality of the control in this experiment. Relative liver weights of males fed 2.5 ppm and females fed 12.5 ppm were significantly greater than controls.

Deichmann et al. (1970) fed groups of 30 male and 30 female Osborne-Mendel rats diets containing 0, 20, 30 or 50 ppm aldrin for 2 years. Tremors and convulsions were observed in a few rats in all treated groups, and the number affected was dose-related. The lifespan of high-dose females was shortened, and relative liver weights were increased in male rats at 30 and 50 ppm.

Fitzhugh et al. (1964) fed groups of 12 male and 12 female Osborne-Mendel rats diets containing 0, 0.5, 2, 10, 50, 100 or 150 ppm aldrin for 2 years. Survival was reduced at $\geq$50 ppm. Increased relative liver weights and microscopic liver lesions occurred at all doses. The liver lesions were minimal in rats fed 0.5 ppm aldrin and pronounced at $\geq$50 ppm.

Hodge et al. (1967) summarized available aldrin toxicity studies and attempted to define thresholds for various effects in different species. The most sensitive effect of aldrin was increased relative liver weight in rats, which occurred at a concentration of 0.5 ppm in the diet for 2 years.

Histopathological liver effects occurred at 2 ppm aldrin in the diet for 2 years, but not at 0.5 ppm. This is in contrast to the observation by Fitzhugh et al. (1964) who noted minimal liver lesions in rats fed diets containing 0.5 ppm aldrin for 2 years. In dogs, increased relative liver weights and histopathological liver effects occurred at 3 ppm aldrin in the diet for 15 months, but not at 1 ppm. A dietary concentration of 10 ppm for 2 years caused histopathological changes in the liver of mice.

Most of the information concerning chronic oral toxicity of aldrin is provided by studies that are primarily concerned with the potential for carcinogenicity. These studies are discussed in more detail in Section 4.2.

3.2.2. Inhalation. Avar and Czegledi-Janko (1970) studied occurrence of neurological signs and symptoms in a group of 15 male workers occupationally exposed to aldrin for $\leq$5 years. Some workers with whole blood dieldrin concentrations 0.10 ppm had signs of aldrin poisoning, but others had no signs at higher blood levels (0.25 ppm). In three severely affected men, symptoms ceased within 7 months after cessation of exposure. Dieldrin, the epoxide of aldrin, is the predominant metabolite of aldrin in animals.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Treon and Cleveland (1955) reported results of a 3-generation study in which aldrin was fed to groups of Carworth rats at dietary concentrations of 0, 2.5, 12.5 or 25 ppm. At 12.5 or 25 ppm, aldrin caused reduced numbers of pregnancies, and increased pup mortality during the suckling period. Effects at 2.5 ppm were described as "slight to moderate." Litter size was unaffected at any concentration.

Hodge et al. (1967) and Clegg (1979) summarized several studies concerning reproductive effects of aldrin. Clegg (1979) reported that postnatal survival was decreased in the F_{2a}, F_{1b} and F_{2b} generations of mice fed

3, 5 or 10 ppm aldrin in the diet. Hodge et al. (1967) attempted to define thresholds for reproductive effects. Estrus cycles of rats were disturbed when they were fed aldrin at a dietary concentration of 20 ppm, but not at 5 ppm. In dogs, 8 ppm aldrin in the diet caused increased pup mortality. None of the studies summarized by Hodge et al. (1967) indicated that aldrin caused any teratogenic effects in rats or dogs.

Ottolenghi et al. (1974) conducted a study in which pregnant golden hamsters or CD-1 mice were given single oral doses of 50 or 25 mg/kg, respectively. Hamsters were treated on days 7, 8 or 9 of gestation and mice on day 9. Treatment on day 7 or 8 caused a significant increase in fetal deaths in hamsters. Reduced fetal weight occurred in treated hamsters. Hamsters treated on day 8 had the highest incidence of anomalies (open eye, webbed foot, cleft palate, etc.) Teratogenic effects also occurred in treated mice.

3.3.2. Inhalation. Data concerning teratogenic or reproductive effects of aldrin in inhalation exposures could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

U.S. EPA (1980a) noted that since aldrin is metabolized by hepatic MFOs, any inducer or inhibitor of these enzymes would affect the metabolism of aldrin. Deichmann et al. (1968) found that tissue DDT concentrations were increased in dogs given DDT and aldrin compared with those given DDT alone; no explanation was given for this observation. Rats pretreated with a diet containing 250 ppm hexachlorobenzene for 4 weeks retained less radioactivity from an intraperitoneal injection of 5 mg/kg radiolabeled aldrin than rats that were not pretreated with hexachlorobenzene (Clark et al., 1981).

Williams et al. (1967) reported that aldrin pretreatment by intraperitoneal injection reduced the acute oral toxicity of Banol and Mobam, two carbamate insecticides. Triolo and Coon (1966) and Triolo et al. (1970) found that aldrin pretreatment reduced the toxicity of parathion and paraoxon. Aldrin failed to protect against the antichloinesterase effects of OMPA and neostigmine (Triolo and Coon, 1966).

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding carcinogenicity of aldrin to humans from oral exposure could not be located in the available literature.

4.1.2. Inhalation. Versteeg and Jager (1973) reported results of a study of 233 pesticide workers at a plant in Holland. These workers were exposed to aldrin and dieldrin for up to 12.3 years, with a mean exposure of 6.6 years and an average time since the end of exposure of 7.4 years. Van Raalte (1977) published a follow-up study on these workers, and reported that no increase in incidence of any type of cancer was observed. U.S. EPA (1980a) has criticized these studies because of the small sample size, short exposure time and short observation period.

4.2. BIOASSAYS

4.2.1. Oral. The available data from carcinogenicity bioassays with aldrin are summarized in Table 4-1. Negative results were obtained in three carcinogenicity studies with Osborne-Mendel rats (Deichmann et al., 1970; Fitzhugh et al., 1964; NCI, 1977). In contrast, the NCI (1977) study using mice yielded positive results as did the Davis (1965) and Davis and Fitzhugh (1962) studies. U.S. EPA (1980a) noted that mice appear to be the species most susceptible to carcinogenic effects of aldrin. The U.S. EPA (1986b) evaluated these studies and felt that the Deichmann et al. (1970) study was an inadequate test of carcinogenicity; therefore, this study will not be further discussed.

In the NCI (1977) study using rats, groups of 50 male and 50 female Osborne-Mendel rats were fed diets containing 30 or 60 ppm aldrin for 74 weeks, followed by a 37- to 38-week observation period. Matched controls consisted of 10 rats/sex, and pooled controls used for statistical analyses

TABLE 4-1

Summary of Carcinogenicity Data for Aldrin

Species/Strain	Sex/Number/Group	Dose, Duration	Length of Study	Compound Purity	Effects	Reference
Rats/Osborne-Mendel	50/sex/treated group, 10/sex matched controls, 68 males and 70 females in pooled control group	0, 30, 60 ppm diet for 74 weeks	111-113 weeks	technical	Decreased body weights in treated rats relative to controls; hyperexcitability in treated rats; increased combined incidence of follicular-cell adenoma and carcinoma of thyroid in males (3/7 matched controls, 4/48 pooled controls, 14/38 low dose, 8/38 high dose) and females (matched controls 1/9, pooled control 3/52, low dose 10/59, high dose 7/46), significant only in low dose group when compared with pooled controls; increased incidence of adrenal cortical adenoma in low dose (8/45) but not high dose (1/48) females relative to pooled controls (0/55)	NCI, 1977
Rats/Osborne-Mendel	12/sex/group	0, 0.5, 2,10, 50, 100, 150 ppm diet for 2 years	2 years	99+%	Reduced survival at ≥50 ppm; high incidence of multiple site tumors at lower concentrations; liver lesions in all treated rats	Fitzhugh et al., 1964
Rats/Osborne-Mendel	30/sex/group (100/sex for controls)	0, 20, 30, 50 ppm diet for 2 years	2 years	technical (95%)	Dose-related tremors and convulsions, reduced survival in treated rats, increased relative liver weights at 30 and 50 ppm, increased liver necrosis but decreased incidence of liver tumors in treated rats	Deichmann et al., 1970
Mice/B6C3F1	50/sex/treated group, 20 males and 10 females matched control group, 112 males and 89 females in pooled control groups	0, 3, 6 ppm (females) 0, 4, 8 (males) ppm in the diet for 80 weeks	90-93 weeks	technical	Dose-related mortality in females; hyperexcitability in treated mice; significant dose-related increase in hepatocellular carcinomas in males (3/20 matched controls, 17/92 pooled controls, 16/49 low dose, 25/45 high dose)	NCI, 1977

TABLE 4-1 (cont.)

Species/Strain	Sex/Number/Group	Dose, Duration	Length of Study	Compound Purity	Effects	Reference
Mice/C$_3$HeB/Fe	215 fed 10 ppm, 211 controls "approximately" equally divided by sex"	0 or 10 ppm diet for 2 years	2 years	NR	Reduced survival, increased hyperplasia and hepatomas in treated mice. 9/134 in controls, 35/151 in treated. Reevaluation indicated most of the tumors were carcinomas.	Davis and Fitzhugh, 1962; Epstein, 1975
Mice/C$_3$H	100/sex/group	0 or 10 ppm diet for 2 years	2 years	NR	Hepatomas 27/200 control, 65/200 treated. Reevaluation indicated most tumors were carcinomas.	Davis, 1965; Epstein, 1975

NR = Not reported

consisted of matched controls plus 58 untreated males and 60 untreated females from other studies. Hyperexcitability and reduced body weights relative to controls occurred in treated rats during the second year of the study. The combined incidence of follicular cell adenoma and carcinoma of the thyroid was increased in male and female rats, but this increase was significant only in low-dose males (14/38, p=0.001) and low-dose females (10/39, p=0.009) when compared with pooled controls (4/46 males and 3/52 females). Cortical adenoma of the adrenal gland was increased in the low-dose females (8/45) but not in high-dose females (1/48) compared with pooled controls (0/55, p=0.001). In the absence of significant increases in any tumor relative to matched controls, NCI (1977) concluded that none of the observed tumors in rats could be associated with aldrin treatment.

In the Fitzhugh et al. (1964) study, as described by U.S. EPA (1986b), aldrin (>99% purity) was administered to 12 male and 12 female Osborne-Mendel rats in the diet at dose levels of 0, 0.5, 2, 10, 50, 100 or 150 ppm for a period of 2 years. The rats were 3 weeks of age when aldrin diet was started.

There was no significant effect on growth rate. However, survival was markedly decreased in aldrin groups at 50 ppm or more. Increases in liver-to-body weight ratio were reported at all dose levels and were statistically increased from controls ($p<0.05$) at 10 ppm and greater in males and at all dose levels for females. Chronic nephritis, which occurred more commonly in males than females, was reported for high-dose levels.

Only 68% of all animals were examined histologically. Total tumor incidence (all doses combined) in aldrin-treated animals was 36% compared with an incidence in controls of 18%. However, the increase was particularly large among rats at the lower dosage levels. The lower incidence at higher doses may have been related to the decreased survival at the high doses.

There was no predominant tumor type with tumors in various organs including the lungs, breast and lymphoreticular system. Although no hepatomas or hepatocellular carcinomas were diagnosed, a high incidence of "chlorinated insecticide" lesions were observed at 50 ppm and above.

In the NCI (1977) mouse study, groups of 50 male and 50 female B6C3F1 mice were fed diets containing 3 or 6 ppm (females) or 4 or 8 ppm (males) for 80 weeks followed by a 10- to 13-week observation period (NCI, 1977). Matched controls consisted of 10 untreated females and 20 untreated males; pooled controls consisted of matched controls plus 79 untreated females and 92 untreated males from other experiments. There was a significant dose-related increase in the incidence of hepatocellular carcinomas in male mice (matched controls 3/20, pooled controls 17/92, low-dose 16/49, high-dose 25/45) when compared with matched controls ($p=0.001$) or pooled controls ($p<0.001$). NCI (1977) concluded that aldrin was carcinogenic to male B6C3F1 mice, causing hepatocellular carcinomas.

Davis and Fitzhugh (1962) alluded to a previous 2-year aldrin mouse feeding study that raised the suspicion of tumorigenicity of aldrin although the results were considered inconclusive because the majority of the animals were not available for pathologic examination. No reference was provided and no further information could be found on that study.

In this study, as reviewed by U.S. EPA (1986b), a group of 215 C_3HeB/Fe mice were fed a dietary mixture containing 10 ppm aldrin (purity not specified) for a period of up to 2 years. The control group consisted of 217 mice. The number of mice/sex was not given but they were approximately equally divided by sex. Mice that died during the experiment were necropsied, as were all 2-year survivors. The extent of pathology examination was not clear. Tissues from animals with gross lesions and from some grossly

normal mice were preserved. After fixation, the tissues were reexamined and were selected for microscopic study. Slides were prepared from all gross lesions in which neoplasia was suspected, from lungs of mice that had hepatic masses, and also from some animals that had gross pneumonia, intussusceptions, or certain other incidental gross abnormalities. No breakdown was provided as to actual tissues examined.

The average survival of the aldrin-treated groups was ~2 months less than controls. Intercurrent diseases, pneumonia and intestinal parasitism were present and may have influenced the long-term survival rate.

Results, reported for both sexes combined, indicated a statistically significant ($p<0.001$) increase in the incidence of hepatomas (hepatic cell adenomas) in the treated animals as compared with controls. Only one other tumor (lung) was reported in the aldrin group. The incidence of hepatomas, based on necropsied mice, was 23% in the aldrin group and 7% in controls. The hepatic cell adenomas were described as expanding nodules of hepatic parenchymal tissue, usually with altered lobular architecture, and morphologically ranging from very benign lesions to borderline carcinomas. The authors concluded that aldrin had significantly increased the incidence of histologically benign liver tumors. Dr. M. Reuber conducted an independent reevaluation of the liver lesions and considered most of the hepatomas to be liver carcinomas. Drs. Popper, Farber and Firminger concurred with Reuber's evaluation (Epstein, 1975). The value of this study was compromised by the poor survival rate, lack of detailed pathology, loss of a large percentage of the animals to the study, and failure to treat the results in males and females separately. Despite these inadequacies, the study revealed evidence for hepatocarcinogenicity of aldrin in C_3H mice.

As a followup to the previous study, Davis (1965), as reviewed by U.S. EPA (1986b), administered aldrin (purity not specified) at 0 or 10 ppm in the diet to groups of 100 male and 100 female C_3H mice for 2 years. The pathology examination was similar to that conducted in Davis and Fitzhugh (1962). Again, survival in the treated group was reduced compared with the control group, although no breakdown of data by sex and by time of death was given. There was no indication as to the time of tumor detection or deaths in treated versus control groups. The incidence of hepatic hyperplasia and benign hepatomas in the aldrin group was approximately double that of controls, whereas the number of hepatic carcinomas was about the same. Dr. Reuber also reevaluated the liver lesions from this study and concluded that most of the hepatomas were actually carcinomas. Drs. Popper, Farber and Firminger concurred in Reuber's diagnosis (Epstein, 1975).

Some of the same deficiencies seen in the 1962 FDA study were also evident in this one; namely, a lack of detailed pathology examination and failure to present data according to sex. However, the survival at 18 or 24 months was acceptable in the controls. The evidence for an oncogenic response (whether benign or malignant) is substantial in male and female C_3H mice.

4.2.2. Inhalation. Carcinogenicity bioassays for aldrin in which inhalation exposures were used could not be located in the available literature.

4.3. OTHER RELEVANT DATA

U.S. EPA (1980a) noted that data concerning mutagenicity of aldrin were limited, but that the data concerning dieldrin might be sufficient since aldrin is readily converted to dieldrin in both *in vivo* and *in vitro* systems. Several studies reviewed by U.S. EPA (1980a) indicated that aldrin/dieldrin gave predominantly negative results in mutagenicity assays

with microorganisms. In a review of several studies, Ashwood-Smith (1981) noted that aldrin was generally not mutagenic in bacterial assays, and that most mammalian studies were difficult to interpret because of a lack of positive controls or a dose-response relationship. A more recent review by Khan and Dev (1982) stated that aldrin was not mutagenic in bacteria and yeast.

4.4. WEIGHT OF EVIDENCE

Aldrin can be placed in EPA Group B2, Probable Human Carcinogen, using the U.S. EPA (1986a) guidelines for carcinogen risk assessment. This category applies to compounds for which there is sufficient evidence of carcinogenicity in animals in the absence of human data. In this case, the sufficient animal evidence consists of a definitive malignant tumor response in independent studies that included different strains of the same species (mouse) (U.S. EPA, 1986b).

Aldrin was classified by IARC (1982) in Group 3, chemicals that cannot be classified as to their potential carcinogenicity in humans. The database provides limited evidence of carcinogenicity in animals and inadequate evidence of carcinogenicity in humans.

5. REGULATORY STANDARDS AND CRITERIA

U.S. EPA (1980a) derived cancer-based ambient water quality criteria for aldrin using a potency factor calculated from data for incidence of hepatocellular carcinomas in male mice in the NCI (1977) bioassay. The q_1^* for aldrin was 11.45 $(mg/kg/day)^{-1}$. The resulting criteria corresponding to an incremental increase of lifetime cancer risk of 10^{-5}, 10^{-6} and 10^{-7} are 0.74, 0.074 and 0.0074 ng/ℓ, respectively, for exposure to contaminated water and ingestion of contaminated aquatic organisms. The criteria are 0.79, 0.079 and 0.0079 ng/ℓ if only consumption of contaminated aquatic organisms is considered. Because aldrin is rapidly metabolized to dieldrin in fish, these criteria were calculated by application of a factor based on the carcinogenic potency of dieldrin as well as that of aldrin.

ACGIH (1986) recommended a TLV of 0.25 mg/m^3 for aldrin. This value was designed to protect against liver injury, but ACGIH (1986) noted that it had only limited supporting data. The OSHA (1983) standard is also 0.25 mg/m^3.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

Because aldrin is classified as a carcinogen, no RfD_S (formerly AIS) values for oral or inhalation exposures will be calculated.

6.2. REFERENCE DOSE (RfD)

Because aldrin is classified as a carcinogen, no RfD (formerly AIC) values for oral or inhalation exposures will be calculated.

6.3. CARCINOGENIC POTENCY (q_1*)

6.3.1. Oral. U.S. EPA (1986b) performed a quantitative carcinogenicity risk assessment for aldrin. The following text was adapted from this recent document.

Three data sets are suitable for quantitative risk estimation. These are both male and female C_3H mice in the Davis (1965) study as reevaluated by Reuber and cited in Epstein (1975), and male B6C3F1 mice in the NCI (1978) bioassay.

Using these data sets and the linearized multistage model of Crump (U.S. EPA, 1980c), three potency esimates, ranging from 23 down to 12 $(mg/kg/day)^{-1}$, with a geometric mean of 17 $(mg/kg/day)^{-1}$ were calculated. Because humans may be as sensitive as the most sensitive animal species, the potency for the general population is estimated at 17 $(mg/kg/day)^{-1}$.

These estimates are plausible upper bounds for the increased cancer risk from aldrin, meaning that the true risk is not likely to exceed these estimates and may be lower.

Review of the CBI file for aldrin did not reveal any information that would affect this assessment.

6.3.2. Inhalation. Inhalation data for aldrin were insufficient to perform a quantitative risk assessment.

TABLE 6-1

Cancer Data Sheet for Derivation of q_1^*

Compound: aldrin

Reference: NCI, 1978; U.S. EPA, 1986b

Species, Strain, Sex: mice, B6C3F1, male

Body weight: 0.035 kg (measured)

Length of exposure (le) = 80 weeks

Length of experiment (Le) = 90 weeks

Lifespan of animal (L) = 90 weeks

Tumor site and type: hepatocellular carcinomas

Route, vehicle: oral, diet

Experimental Doses or Exposures (ppm in diet)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested or Examined
0	0	17/92
4	0.52	16/49
8	1.04	25/45

Human $q_1^* = 12\ (mg/kg/day)^{-1}$

TABLE 6-2

Cancer Data Sheet for Derivation of q_1^*

Compound: aldrin

Reference: Davis, 1965; U.S. EPA, 1986b

Species, Strain, Sex: mice, C_3H, female

Body weight: 0.030 kg (assumed)

Length of exposure (le) = 2 years

Length of experiment (Le) = 2 years

Tumor site and type: liver, carcinoma

Route, vehicle: oral, diet

Experimental Dose (ppm)	Transformed Dose (mg/kg/day)	Human Equivalent Dose (mg/kg/day)	Incidence No. Responding/ No. Examined
0	0	0	2/53
10	1.3	0.104	72/85

Human $q_1^* = 23\ (mg/kg/day)^{-1}$

TABLE 6-3

Cancer Data Sheet for Derivation of q_1^*

Compound: aldrin

Reference: Davis and Fitzhugh, 1962; U.S. EPA, 1986b

Species, Strain, Sex: mice, C_3H, male

Body weight: 0.030 kg (assumed)

Length of exposure (le) = 2 years

Length of experiment (Le) = 2 years

Tumor site and type: liver, carcinoma

Route, vehicle: oral, diet

Experimental Dose (ppm)	Transformed Dose (mg/kg/day)	Human Equivalent Dose (mg/kg/day)	Incidence No. Responding/ No. Examined
0	0	0	22/13
10	1.3	0.104	75/91

Human $q_1^* = 18\ (mg/kg/day)^{-1}$

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APPENDIX

Summary Table for Aldrin

Route	Species/ Strain/Sex	Experimental Exposure/Dose	Effect	q_1^* $(mg/kg/day)^{-1}$	Reference
Oral	mice/B6C3F1/ male, C_3H/ male, C_3H/ female	Dietary exposure for up to 2 years. The geometric mean q_1^* from three separate studies was utilized.	hepatocellular carcinoma	17	NCI, 1977; Davis and Fitzhugh, 1962; Epstein, 1975; Davis, 1965; U.S. EPA, 1986b